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(54) Pharmaceutical preparation for endermic use.

(57) A pharmaceutical preparation for endermic application is disclosed which comprises indomethacin and at least one solubilizer selected from C_{10} terpenoids and C_{10} phenols. The addition of these solubilizers in small quantities significantly increase the solubility and stability of indomethacin in various solvents and thus produce indomethacin solutions which can be used *per se*, or incorporated in a wide variety of bases to provide endermically-applicable preparations of various forms.

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"PHARMACEUTICAL PREPARATION FOR ENDERMIC APPLICATION"

This invention relates to a novel pharmaceutical preparation containing indomethacin for endermic application.

Indomethacin is an excellent non-steroidal analgesic and antiphlogistic agent. It is, however, barely soluble in water, or in various solvents which are generally usable as bases for endermic application. Indomethacin is slightly soluble in benzyl alcohol, tetrahydrofuran, dimethylsulfoxide, and dimethylformamide. The indomethacin solutions produced suffer from difficulties in the formation of a preparation suitable for endermic application, from both the viewpoints of the concentration and the potency of indomethacin. Hitherto, therefore, indomethacin has been generally administered in the form of an oral preparation.

The present inventors have made many studies of preparations of indomethacin for endermic application and have already succeeded in obtaining an endermically-applicable preparation having excellent absorptivity through the skin by incorporating indomethacin in an alcohol-water

system and then forming the resultant mixture into a gelated ointment, as disclosed in published Japanese Patent Application No. 10886/1981. Such a gelated ointment has been recently marketed and has been found to be very valuable in its clinical application.

The present inventors have conducted continuous research with a view toward developing new dosable forms of the endermically-applicable indomethacin preparation and bases therefor. As a result, it has been discovered that certain terpenoids and phenols can enhance the solubility and stability of indomethacin in bases and hence permit indomethacin to be incorporated in a variety of bases for endermic application. This discovery has led to the present invention.

According to the present invention, therefore, there is provided a pharmaceutical preparation for endermic application, which comprises indomethacin and one or more solubilizers selected from C_{10} terpenoids and C_{10} phenols.

Suitable terpenoids having 10 carbon atoms which are useful as the solubilizer or at least one of the solubilizers in the preparations of the invention include hydrocarbonaceous terpenes, such as limonene, pinene, camphene and cymene;

alcoholic terpenes, such as citronellol, geraniol, nellol, linalol, menthol, terpineol, rosinol, borneol, and iso-borneol; and ketone-type terpenes, such as menthone and camphor. Suitable phenols having 10 carbon atoms useful as the solubilizer or at least one of the solubilizers in the preparations of the invention include thymol, safrole, iso-safrole, eugenol, iso-eugenol and the like. These solubilizers may be used singly or in combination. The content of such solubilizers when used either alone or in combination may vary depending on the content of indomethacin and the type and amount of a solvent used. However, the solubilizers of the invention are capable of producing satisfactory results when incorporated in a total amount of 0.3 - 10% by weight of the preparation.

Suitable solvents for dissolving indomethacin include alcohols, such as ethanol and propanol; mixed alcohol-water systems; glycols such as butylene glycol and propylene glycol; vegetable oils such as olive oil and soybean oil; liquid higher fatty acids such as oleic acid, linoleic acid and linolenic acid; higher alcohols such as octyl alcohol and hexadecyl alcohol; hydrocarbons such as paraffin and squalane; esters of C_4-C_{14} monocarboxylic acids and C_1-C_5 alcohols;

and diesters of C_4-C_{10} dicarboxylic acids and C_1-C_3 alcohols.

A pharmaceutical preparation for endermic application according to the invention may be produced by dissolving indomethacin together with at least one solubilizer in one or more of the above-mentioned solvents, or by further incorporating the solution thus formed in another base for endermic application. Preferably, indomethacin is present in an amount of 0.1 - 5% by weight of the preparation.

Suitable forms of pharmaceutical preparation for endermic application which are obtainable in such manner include, for example, liquid preparations, ointments, gelated ointments, creams, and plasters.

Since the addition of one or more of the solubilizers of the invention in a small amount can significantly increase the solubility and stability of indomethacin in various solvents, the resultant indomethacin solutions may be incorporated in a wide variety of bases for endermic application, thus providing endermically-applicable preparations of various forms. The solubilizers used in the invention are thus extremely effective.

The invention is illustrated by the following

non-limitative examples:

Experiment 1:

Solubility Test on Indomethacin

A large excess of indomethacin was added to each of a number of solvents, followed by addition of one of the solubilizers given in Table 1. The resultant mixture was shaken for 24 hours at 25°C and then subjected to centrifugal separation. The supernatant liquid was collected. The content of indomethacin in the supernatant liquid was determined by the UV method or the HPLC method and compared with that in a supernatant liquid having no stabilizer added thereto. The results are shown in Tables 1 and 2.

Table 1

Solubilizer / Solvent	None (Weight dissolved) (mg/ml)	ℓ-Menthol 3%	ℓ-Menthol 5%	ℓ-Menthol 10%
100% Ethanol	100 (17.4)	130	140	150
80% Ethanol	100 (8.0)	140	200	270
60% Ethanol	100 (2.4)	160	350	440
50% Ethanol	100 (0.75)	350	x	x
Isopropyl myristate	100 (1.3)	210	x	x
Octylodecyl myristate	100 (0.5)	190	x	x
Propanol	100 (7.5)	180	x	x

Note: The figures are expressed in terms of percentage to the weight of indomethacin dissolved without any solubilizer added in their corresponding solvents.

The symbol x indicates that the solubilizer was not dissolved in the solvent.

Table 2

Solvent / Solubilizer	100% Ethanol	80% Ethanol	60% Ethanol	50% Ethanol
None (weight dissolved) (mg/ml)	100 (17.4)	100 (8.0)	100 (2.4)	100 (0.75)
dl-Camphor 3%	120	150	170	270
dl-Camphor 5%	160	190	230	400
dl-Camphor 10%	200	230	390	x
Eugenol 3%	140	160	170	x
Eugenol 5%	400	190	250	x
D-limonene 3%	140	170	x	x
D-limonene 5%	250	200	x	x

Note: The figures and the symbol x have the same significance as given in Table 1.

Preparation Example 1:	(Ointment)	
Indomethacin	0.5	(wt.%)
Geraniol	5.0	
Eugenol	5.0	
Vaseline	80.5	
Solid paraffin	5.0	
Cetanol	2.0	
Isopropyl myristate	2.0	
Preparation Example 2:	(Gelated Preparation)	
Indomethacin	1.0	(wt.%)
ℓ-Menthol	3.0	
Propylene glycol	12.0	
Carboxyvinyl polymer (CARBOPOLE 934)	1.0	
Diisopropanol amine	1.0	
Ethanol	40.0	
Purified water	Balance to 100.0	
Preparation Example 3:	(Liquid Preparation)	
Indomethacin	2.0	(wt.%)
ℓ-Menthol	10.0	
Ethanol	45.0	
Aqueous ammonia (10%)	0.2	
Purified water	Balance to 100.0	

Preparation Example 4: (O/W Cream)

Indomethacin	0.8 (wt.%)
Camphor	2.0
Diisopropyl adipate	20.0
Chrotamiton	2.0
Glyceryl monostearate	10.0
Polyoxyethylene cetyl ether	3.0
Methylparaben	0.1
Propylparaben	0.1
Purified water	Balance to 100.0

Preparation Example 5: (Plaster)

Indomethacin	1.0 (wt.%)
Methyl salicylate	2.0
£-Menthol	3.0
Diethyl sebacate	5.0
Raw rubber	40.0
Zinc flower	20.0
Rosin	29.0

CLAIMS

1. A pharmaceutical preparation for endermic application, characterised in that it comprises indomethacin and at least one solubilizer selected from C_{10} terpenoids and C_{10} phenols.

2. A pharmaceutical preparation according to Claim 1, characterised in that the indomethacin is present in an amount of 0.1 - 5% by weight of the preparation.

3. A pharmaceutical preparation according to Claim 1, characterised in that said solubilizer or solubilizers is or are present in a total amount of 0.3 - 10% by weight of the preparation.

4. A pharmaceutical preparation according to any one of Claims 1 to 3, characterised in that said solubilizer, or at least one of said solubilizers is a C_{10} terpenoid selected from the group: limonene, pinene, camphene, cymene, citronellol, geraniol, nellol, linalol, menthol, terpineol, rosinol, borneol, iso-borneol, menthone and camphor.

5. A pharmaceutical preparation according to any one of Claims 1 to 4, wherein said solubilizer or at least one of said solubilizers is a C_{10} phenol selected from the group: thymol, safrole, iso-safrole, eugenol and iso-eugenol.

6. A process for producing a pharmaceutical preparation as claimed in any one of Claims 1 to 5 comprising the step of dissolving indomethacin in a solvent together with at least one solubilizer selected from C_{10} terpenoids and C_{10} phenols.

7. A process as claimed in Claim 6, characterised in that the solution formed is incorporated in another base for endermic application.